

1920
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J. C. Ward.

Nitroso Derivatives of Phenol Ethers

NITROSO DERIVATIVES OF PHENOL ETHERS

BY

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THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

IN

CHEMISTRY

COLLEGE OF LIBERAL ARTS AND SCIENCES

UNIVERSITY OF ILLINOIS

1920

1920
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UNIVERSITY OF ILLINOIS

.....June 5.....1920.....

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

.....Justus Conrad Ward.....

ENTITLED.....Nitroso Derivatives of Phenol Ethers.....

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF.....Bachelor of Science.....

.....*Oliver Kamm*.....

Instructor in Charge

APPROVED:.....

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ACKNOWLEDGMENT

The author wishes to thank Dr. Oliver Kamm, under whose supervision this work was carried on, for the helpful suggestions the latter has offered during the progress of the investigations and the writing of the thesis.



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TABLE OF CONTENTS

	Page
I. Introduction.....	1
II. Historical Part.....	3
III. Theoretical.....	7
IV. Experimental Part.....	10
Preparation of p-Nitrosophenol.....	10
Formation of Quinhydrones in the Preparation of p-Nitrosophenol.....	10
Preparation of Dichloraminophenol.....	11
Investigation of Possible Yields of the Methyl and Ethyl Derivatives of p-Nitroso- phenol.....	11
Preparation of the β -Chloro-ethyl and the n-Butyl Derivatives of p-Nitrosophenol.....	13
Reduction of the Nitroso Group in the Various Substituted Ethers.....	14
Heat Decomposition Products of the Methyl and Ethyl Derivatives of p-Nitrosophenol.....	15
V. Summary.....	16
VI. Bibliography.....	17

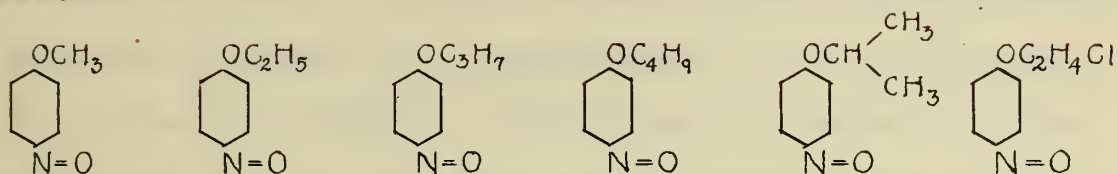
NITROSO DERIVATIVES OF PHENOL ETHERS

I. Introduction.

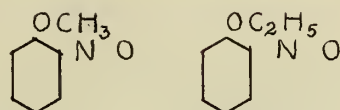
Nitroso derivatives of phenol ethers have been sought since early in that period of organic chemistry, which was characterized by an interest in the structure of chemical compounds. It was logically supposed to be possible to prepare a series of substances in which the acidic hydrogen of a nitroso phenol would be replaced by a hydrocarbon radical. Repeated attempts to accomplish this substitution were made, yet the products obtained always failed to show any indications of possessing the structure, which was expected of them. Consequently the study of this problem was interesting from the viewpoint of finding where-in the earlier investigators had failed.

Through a series of researches carried on under the direction of Doctor Oliver Kamm, at the University of Illinois, there was developed a method of preparation for the simpler compounds of the series; and it was the desire that these further investigations would discover improved methods for securing the known ethers; and that these processes could be applied to the preparation of the similar, but more complex nitroso derivatives.

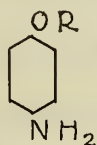
In short, we hoped to prepare the following series of compounds:--



And at least the first two members of the corresponding series of ortho derivatives, which would have this structure:--



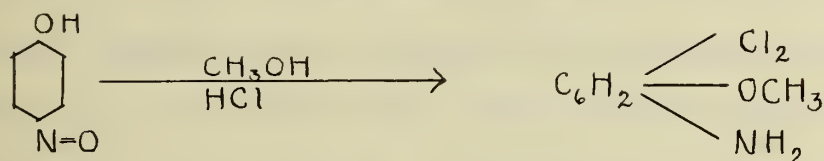
It was then wished to reduce the nitroso group, in each of these compounds, to an amino group, without affecting the ether portion of the molecule. This would yield a series of this general type:--



Since in most cases the resulting amines would be liquids, it would be necessary to prepare suitable solid derivatives in order to obtain satisfactory constants. Consequently, owing to the convenience of securing them, the acetyl derivatives were selected. The making of these compounds would complete the evidence which would prove the ether structure of the nitroso derivatives studied.

II. Historical.

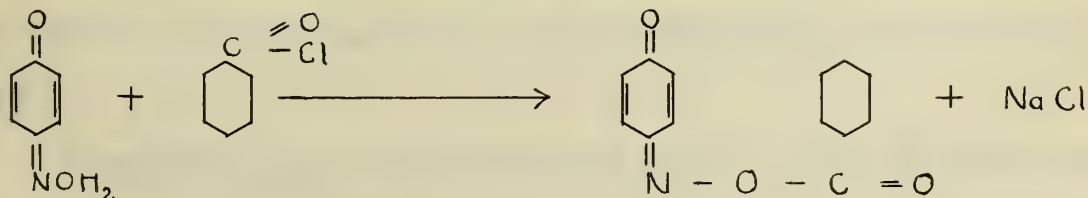
The earliest literature, which mentions any replacement of the phenolic hydrogen in a nitrosophenol, is an article published by C. Jaeger in 1875. (1) In this paper, the author gives the reactions of methyl alcohol, saturated with hydrogen chloride, on p-nitrosophenol. A very remarkable series of changes occur simultaneously, with the final compound being an amine melting at 71.5 °C.



The analogous ethyl compound was found to be a substance melting at 46 °C.

The same investigator obtained a similar amine, (1) containing a free phenolic group, by treating the p-nitrosophenol with hydrogen chloride in solution in dry ether. The melting point of this compound was 175 °C.

In the years following 1875, little was published on this subject until 1884, when J. F. Walker wrote on the preparation of various additional compounds. (2) The first of these was benzoylnitrosophenol, which was made by the interaction between sodium nitrosophenolate and benzoyl chloride.

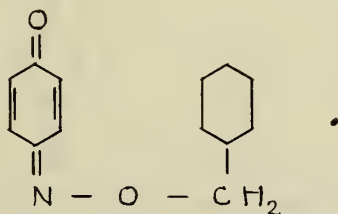


His other compounds were the ethylnitrosophenolcarboxylate, C₆H₄(No)OCOOEt, melting point 105 °C.; and the corresponding

methyl compound, which melted at 137⁰ C.

J. L. Bridge was the next investigator whose work dealt with the study of the reactions of nitrosophenol. In a paper published in 1892,⁽³⁾ the author described a compound, the methoxide of quinoneoxime, $C_6H_4ONOCCH_3$, which he prepared by treating the silver salt of nitrosophenol with one and one-fourth the theoretical amount of methyl iodide and refluxing for two of three hours. The purified, flat, yellow needles melted at 83⁰ C. Bridge noted that if his crystals were not pure they decomposed quickly, turning first green and then brown. The ethoxide was prepared in an analogous way and a product, which melted at 30⁰ C. was easily isolated. A dibromide derivative of the methoxide was prepared by treating the chloroform solution of it with a molecular amount of bromine. Colorless, flat crystals, which softened at 113⁰ C. and melted at 118⁰ C., were obtained.

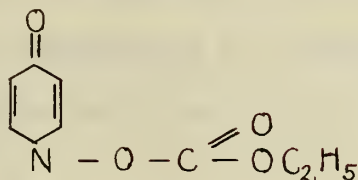
As a proof of the structure of these substances, Bridge found that benzylhydroxylamine converts quinone quantitatively into



which is identical with the compound, that he obtained by treating the sodium or silver salts of p-nitrosophenol with benzyl chloride.

Continuing his investigations into a study of the larger molecular compounds,⁽³⁾ Bridge prepared ethylquinoneoximecarboxylate, which he considered possessed the following structure, by suspending molecular proportions of the silver nitrosophenol and

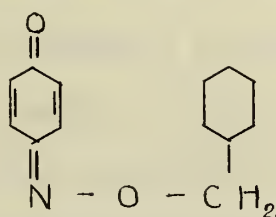
ethylchloroformate in absolute ether, and gently heating the mixture for a few hours.



This compound was yellow with a melting point of 110° C.

Another derivative of quinoneoxime was obtained when Bridge treated an alkaline solution of p-nitrosophenol, or even the dry sodium p-nitrosophenolate, with benzoyl chloride. Pale yellow needles, which melted at 172-174° C., were formed. The alcoholic solution of these crystals possessed a green color, which was hardly as intense as that given by a solution of the nitrosophenol itself in alcohol.

The benzyl ether of quinoneoxime was formed in a similar manner, by heating a suspension of silver nitrosophenol and benzyl chloride in absolute ether for several hours. The compound, whose formula was found to be



crystallized in yellow rectangular or rhombic plates, which melted at 63.5° C. When this compound was treated with tin and hydrochloric acid, p-amidophenol was formed, together with a large amount of benzyl chloride.

From the formulae given in the discussion of Bridge's work, one sees that the true ethers of p-nitrosophenol were not considered by the original articles. In fact no proof of the existence of "true" ethers was known until the work of A. Baeyer

(4)

and E. Knorr was published in 1902.

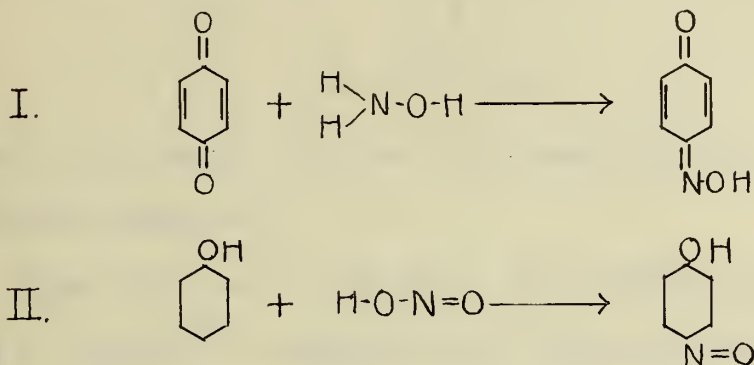
In that work, the authors were successful in obtaining the methyl ether of p-nitrosophenol by treating p-anisidine with Caro's reagent. The product existed in blue-green crystals whose melting point was 32-34 C.

The same green compound was studied in the following year (5) by A. Rising, who prepared p-anisolhydroxylamine and oxidized it in an ice-cold solution to the nitroso material by agitating it with ferric chloride. The melting point of this substance, which the author claimed was a very pure product, was 23 C. In an exactly similar manner, (5) the ethyl ether was obtained by oxidizing a solution of the freshly prepared p-nitrosophenetol with ferric ^{hydroxylamine} chloride. The melting point of this ethyl ether was 33-34 C.

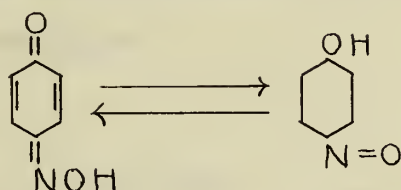
This covers the published material, which has any relation to the study of the nitroso derivatives of phenol ethers. From the methods reviewed for the preparation of these compounds, it would seem that difficulties would be encountered in attempting to substitute for the phenolic hydrogen a hydrocarbon radical, without first preparing a salt of the acid, and then condensing with a chloride; still direct methods of performing such a substitution have been worked out in this laboratory.

III. Theoretical

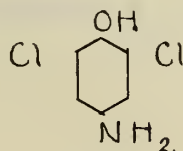
p-nitrosophenol may be prepared not only by the substitution of the nitroso group into phenol (Equation II), but also by the action of hydroxylamine upon p-benzoquinone (Equation I.).



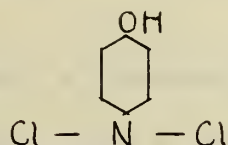
The products of the two reactions are, however, identical, thus suggesting the following equilibrium:



The results of J. L. Bridge's work were such that he felt justified in claiming that p-nitrosophenol always reacted as if it possessed the oxime structure; and to make the further assertion that tautomerism was impossible. This statement was made very positively, although C. Jaeger(1) had in 1875, succeeded in isolating, by the action of hydrochloric acid on p-nitrosophenol, a compound to which he assigned the structure

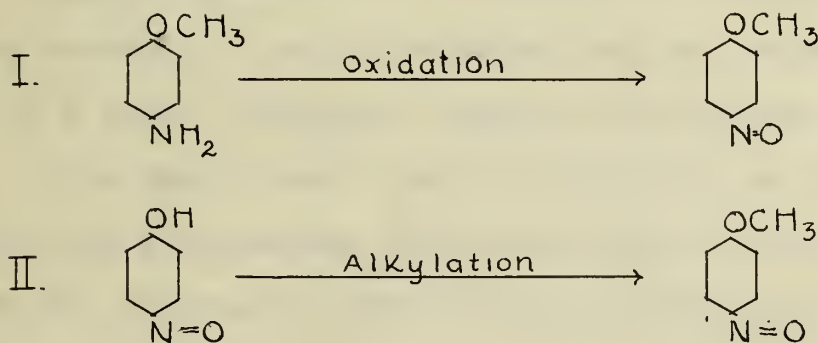


At present, one will not agree exactly with this structure of the compound, since it would be more logical to expect the chlorine atom to enter the 3,5 positions, due to the fact that they probably rearrange from an intermediate compound of this type.



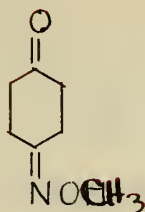
Still there is no doubt but that the phenolic group existed as such in the initial compound.

Since the time of Bridge, the results obtained by A. Baeyer and E. Knorr⁽⁴⁾, together with the work done in this laboratory have definitely determined the fact that p-nitrosophenol reacts in the nitroso form and yields its "true" substituted ethers. Proof of that fact is given by the possibility of isolating identical products from the two reactions.

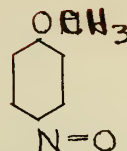


Since both the methyl ether of quinone oxime (~~I~~^{*}) and the methyl derivative of p-nitrosophenol (II.) exist, the question^{is} as to whether it might not be possible to shift from one structure to the other.

*Formula I on the following page.

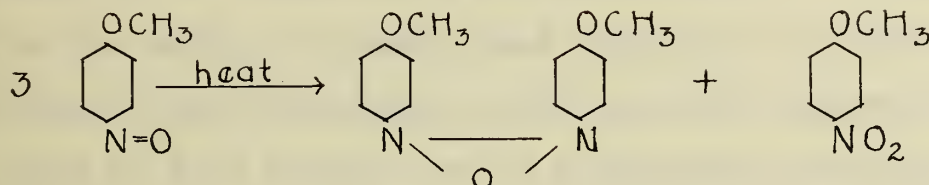


Yellow M.P. 83°
I



Green M.P. 23°
II

Attempts to accomplish such a rearrangement were made by heating compound II. It was found that a yellow substance was formed; but examination proved this material to be azoxyanisole, which must have resulted from a reaction such as



This reaction, and the one which gives the analogous product azoxyphenetol, indicate clearly that the original substances react in the nitroso form.

Finally, however, the formation of quinhydrones, consisting of one molecule of p-nitrosophenol and two molecules of phenol, combined in a stable compound, suggests the quinone formula.

It is easily seen that no conclusion can be reached which agrees with the experimental data; and which at the same time does not assume two tautomeric forms for p-nitrosophenol.

IV. Experimental Part.

Preparation of p-Nitrosophenol

Bridge's directions⁽⁶⁾ for the preparation of p-nitrosophenol were followed, and a satisfactory product was usually obtained. The yields secured were so much lower than those claimed as possible by Bridge, being only sixty-five to sixty-seven percent of the theoretical, that ^{there is} a question as to what the originator of the method meant by an "eighty-five per cent yield". If eighty-five percent of the weight of phenol used was meant, we checked his work quite closely, since the yields obtained here, converted to that basis, would be from eighty-five to eighty-seven percent.

Formation of Quinhydrones in the Preparation of p-Nitrosophenol.

In one preparation of p-nitrosophenol by Bridge's method,⁽⁶⁾ a glistening, dark-brownish compound was formed. It completely ignited off a piece of platinum foil; still it was quite insoluble in ether, differing in that respect very markedly from ordinary p-nitrosophenol. This extraordinary insolubility, together with the unusual appearance of the compound attracted considerable interest, so the substance was analyzed.

It was organic, the ignition test had proven that part. And it was on the assumption that some combination between p-nitrosophenol and phenol had been accomplished that a series of combustions were made. From the results of these analyses, it was concluded that a quinhydrone, consisting of one molecule of p-nitroso-

phenol and two of phenol, had been formed.

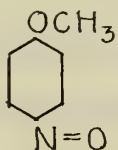
Analysis	c.c. N ₂ in compound	c.c. N ₂ theoretical
I.	8.90	9.10
II.	9.00	9.10

Preparation of Dichloraminophenol

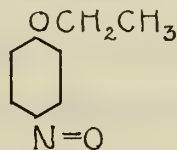
It was thought advisable to duplicate the work of C. Jaeger in isolating the 2-6-dichlor-4-amino-phenol, before attempting any original work. Dry hydrochloric acid gas was passed into ether to saturation, and the cold solution added to p-nitrosophenol, with shaking. The ether solution was washed with dilute sodium hydroxide to free the amine, and to remove the excess p-nitrosophenol. Upon evaporating the washed ether layer, a grayish white solid separated, the melting point of which corresponded closely to that obtained by Jaeger, 174-177° C.

Investigation of Possible Yields of the Methyl and of the Ethyl Derivative of p-Nitrosophenol

In the next place, it was desired to improve the yields of



and



which had been obtained by the process of condensing methyl and ethyl alcohols with p-nitrosophenol. Varying concentrations of

alcohol were used, running from barely enough to dissolve two grams of the nitroso material, up to five times the amount required for solution. In no case was the purified product obtained in a yield of more than fifty percent of the theoretical. Also, at no time, did the increase in alcohol concentration affect the yield to any appreciable extent.

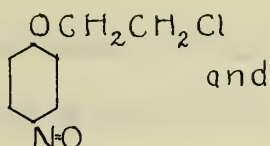
Failing to secure results in this way, an attempt was made to determine the effect of varying both the amount and type of dehydrating agent used, at all concentrations. Some time was spent in these investigations without any improvement being obtained. The dehydrating agents tried were sulphuric acid and phosphoric anhydride. The sulphuric acid was varied from two drops to two cubic centimeters for two grams of p-nitrosophenol taken in different concentrations of alcohol. The best results were secured by dissolving two grams of p-nitrosophenol in sixteen cubic centimeters of alcohol and adding to the cold solution one-half a cubic centimeter of sulphuric acid. The time factor was noted, and it was found that the yields were practically independent of the period of reaction so long as that time was held within ten or fifteen minutes. In excess of that, the acid decomposed the product and the yields immediately began to decrease.

In working with phosphoric anhydride, the reaction was carried on at the temperature of the boiling alcohol. This allowed the use of smaller concentrations of alcohol, so the amounts tried were varied from five to twenty-five cubic centimeters for two grams of p-nitrosophenol. As in the preceding experiments the concentrations of alcohol produced no variation in the yield of

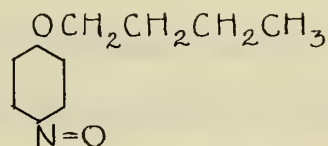
nitroso-ether. Phosphoric anhydride acted quite energetically, when added in amounts greater than a few tenths of a gram at a time, with resulting hydrolysis of the product, and consequently small amounts were always used. At no time was more than one gram added. This work also gave no results, consequently these investigations were terminated with a fifty percent yield as the maximum.

Preparation of the β -Chloro-ethyl and the n-Butyl
Derivatives of p-Nitrosophenol

Continuing the preparations of the nitroso derivatives, it was found that



and



could be prepared by methods quite analogous to those employed for the lower ethers of the series. Two grams of p-nitrosophenol were dissolved in the minimum quantity of alcohol needed for complete solution. This solution was cooled to 0° C. in an ice bath and 0.5 c.c. H₂SO₄ added* with vigorous stirring. After a short time, the green solution was poured into a few cubic centimeters of water in a separatory funnel, and the mixture extracted with ether. The aqueous layer was drawn off and the ether portion, washed with dilute NaOH, until it was no longer colored by the unchanged p-nitrosophenol. The excess NaOH was then removed from the ether layer by washing with a little water. The ether was then evaporated and

*The dehydrating agent may be dissolved in the alcohol, that mixture cooled and then the nitroso added with equally good results.

the product obtained.

In case water soluble alcohols had been used, the pure nitroso ethers were easily obtained. But, in the case of water insoluble alcohols, the p-nitroso-ether was retained in the alcohol solution at the end of the process.

The yields obtained when β -chloro-ethyl alcohol and when n-butyl alcohol were used, were very poor, but the presence of the compounds was unmistakable.

Reduction of the Nitroso Group in the Various
Substituted Ethers.

Since it was known, from previous work done in this laboratory, that the nitroso group of the nitroso derivative of ethyl phenol ether could be readily reduced, it was desired to prepare the amine of the ethers derived from n-butyl alcohol and from ethylene chlorohydrin. Owing to the difficulty experienced in obtaining the latter alcohol, all the attempts at reduction were made on the nitroso ether of the n-butyl derivative.

In working on the preparation of this compound, it was noticed that upon attempting to wash the green ether solution with water, the green color faded to a brown, but that the green was restored by a renewed shaking with sodium hydroxide solution. In view of this fact, it was thought reasonable to try to reduce the compound with zinc and sodium hydroxide. No amine could be extracted from the ether solution, which had been used to separate the products from the zinc residue. Repeated attempts failed to produce any results. The iron and hydrochloric acid method was tried

also without success.

Heat Decomposition Products of the Methyl and
the Ethyl Derivatives of p-Nitrosophenol.

In studying the effects of heat on the nitroso derivatives of various phenol ethers, it was found that merely allowing the ether extraction solution to remain on the water bath until after the liquid had evaporated, was sufficient, in the case of the ethyl derivative, to accomplish a remarkable change. A yellow compound, which melted at 134-136° C. was formed. On investigation it was proven conclusively that it was azoxyphenol. A mixed melting point was taken and no variation from 134-136° C. was noted.

In the same way azoxyanisol was prepared and its identity determined by its melting point, which was 116-117° C. In neither case did the products here isolated show a "milky melt," which is a characteristic of the pure compounds. This fact is easily explained by the fact that no precautions were taken to secure chemically pure materials and doubtless enough foreign substance to prevent this phenomena, was present.

Due to the fact that the n-butyl derivative always existed in a solution of its alcohol, the heat decomposition products were not studied.

V. Summary.

1. Bridge's directions for the preparation of p-nitrosophenol were followed, but his yields were not duplicated.

2. Analyses of a glistening, dark, crystalline product, obtained when running a preparation for p-nitrosophenol, according to Bridge, proved it to be a quinhydrone, containing one molecule of p-nitrosophenol in combination with two molecules of phenol.

3. The reactions, suggested by C. Jaeger in 1875, for the formation of dichloro derivatives of p-aminophenol and p-aminoanisol, were studied and found to be authentic.

4. Effects of varying concentration, time, and dehydrating agents on the preparation of the methyl and ethyl derivatives of p-nitrosophenol, were noted. It was found that the yield was practically independent of concentration and dehydrating agent within short time limits. An increase of the period of reaction beyond ten or fifteen minutes always decreased the yield.

5. β -chloro-ethyl and n-butyl ethers of p-nitrosophenol were prepared.

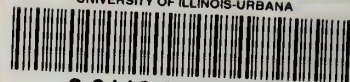
6. Reduction of the nitroso group of the n-butyl derivative was attempted without success.

7. The heat decomposition products of p-nitrosoanisol and of p-nitrosophenetol were obtained, examined, and found to be azoxyanisol and azoxyphenetol, respectively.

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